AMENDMENTS

Please enter the following amendment without prejudice or disclaimer.

In the specification:

Please substitute the following beginning with paragraphs 1 and 2 beginning on page 4, line 1 and ending on page 4, line 26.

In another aspect, the invention provides methods of treating systemic lupus erythematosus (SLE) in an individual, comprising administering to the individual a conjugate comprising (a) a non-immunogenic valency platform molecule and (b) two or more polynucleotides which specifically bind to an antibody from the individual which specifically binds to double stranded DNA, said polynucleotide preferably comprising, consisting essentially of or consisting of the double stranded DNA sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1), wherein the apparent equilibrium dissociation constant (K_D'), or its functional equivalent, for the polynucleotide with respect to the antibody from the individual before or upon initiation of treatment is less than about 1.0 mg IgG per ml, and wherein said K_D' value (or its functional equivalent) is used as a basis for selecting the individual to receive the treatment.

In some embodiments, the treatment methods also include a selection step comprising assessing before initiation of treatment an apparent equilibrium dissociation constant (K_D') (or its functional equivalent) for the epitope, preferably a polynucleotide, contained within the conjugate with respect to antibodies from the individual which specifically bind to double stranded DNA, said conjugate comprising (a) a non-immunogenic valency platform molecule and (b) two or more dsDNA epitopes which specifically bind to an antibody from the individual which specifically binds to double stranded DNA, wherein the individual is selected to receive the treatment if the K_D' (or its functional equivalent) is less than about 1.0 mg IgG per ml. Other, lower K_D' values are described herein which could apply to any of the dsDNA epitopes contemplated for use in treatment, as are percentile ranking with respect to a given patient population as described herein. Preferably, the dsDNA epitopes are polynucleotides, said polynucleotide

preferably comprising, consisting essentially of or consisting of the double stranded DNA sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1).

Please substitute the following for paragraph 1 beginning on page 5, line 6 and ending on page 5, line 16.

In another aspect, the invention provides methods of treating lupus nephritis in an individual, comprising administering to the individual a conjugate comprising (a) a non-immunogenic valency platform molecule and (b) two or more polynucleotides which specifically bind to an antibody from the individual which specifically binds to double stranded DNA, said polynucleotide comprising, consisting essentially of, or consisting of the double stranded DNA sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1), wherein the apparent equilibrium dissociation constant (K_D') (or its functional equivalent) for the polynucleotide in the conjugate with respect to the antibody from the individual before or upon initiation of treatment is less than about 1.0 mg IgG per ml, and wherein said K_D' value (or its functional equivalent) is used as a basis for selecting the individual to receive the treatment.

Please substitute the following beginning with paragraph 2 on page 6, line 10 and ending on page 7, line 4.

In another aspect, the invention provides methods of identifying an individual who may be suitable for treatment for SLE, said treatment comprising administration of a conjugate comprising (a) a non-immunogenic valency platform molecule and (b) two or more polynucleotides which specifically bind to an antibody from the individual which specifically binds to double stranded DNA, said polynucleotide comprising, consisting essentially of, or consisting of the dsDNA sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1), said method comprising measuring the apparent equilibrium dissociation constant (K_D') or its functional equivalent for the polynucleotide used in the conjugate and anti-double stranded DNA antibodies from the individual before or upon

initiation of treatment, wherein an individual is identified by K_D' of less than about 1.0 mg IgG per ml or a functional equivalent thereof.

In another aspect, the invention provides methods of identifying an individual who may be unsuitable for treatment for SLE, said treatment comprising administration of a conjugate comprising (a) a non-immunogenic valency platform molecule and (b) two or more polynucleotides which specifically bind to an antibody from the individual which specifically binds to double stranded DNA, said polynucleotide comprising, consisting essentially of, or consisting of the dsDNA sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1), said method comprising measuring the apparent equilibrium dissociation constant (K_D') or its functional equivalent for the polynucleotide of the conjugate and anti-double stranded DNA antibodies from the individual before or upon initiation of treatment, wherein an individual is identified by K_D' of more than about 1.0 mg IgG per ml or a functional equivalent thereof.

Please substitute the following beginning with paragraph 1 on page 17, line 6 and ending on page 17, line 28.

The terms "polynucleotide" and "nucleic acid", used interchangeably herein, refer to a polymeric form of nucleotides of any length, either ribonucleotides or deoxyribonucleotides. These terms include a single-, double- or triple-stranded DNA, genomic DNA, cDNA, RNA, DNA-RNA hybrid, or a polymer comprising purine and pyrimidine bases, or other natural, chemically, biochemically modified, non-natural or derivatized nucleotide bases. For purposes of this invention, unless otherwise indicated, sequences presented herein denote double stranded sequences. For example, the polynucleotide comprising, consisting essentially of, or consisting of the double stranded sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1) includes the complementary polynucleotide sequence, particularly the sequence 3'-CACACACACACACACACACA-5' (SEQ ID NO:2). It is understood that the double stranded polynucleotide sequences described herein also include the modifications described herein. The backbone of the polynucleotide can comprise sugars and phosphate groups (as may typically be found in RNA or DNA), or modified or

substituted sugar or phosphate groups. Alternatively, the backbone of the polynucleotide can comprise a polymer of synthetic subunits such as phosphoramidates and thus can be a oligodeoxynucleoside phosphoramidate (P-NH2) or a mixed phosphoramidate-phosphodiester oligomer. A phosphorothioate linkage can be used in place of a phosphodiester linkage. In addition, a double-stranded polynucleotide can be obtained from the single stranded polynucleotide product of chemical synthesis either by synthesizing the complementary strand and annealing the strands under appropriate conditions, or by synthesizing the complementary strand *de novo* using a DNA polymerase with an appropriate primer.

Please substitute the following beginning with paragraph 1 on page 26, line 4 and ending on page 28, line 11.

dsDNA epitopes for use in the treatment methods are described herein. In some embodiments, the ds DNA epitope is a polynucleotide, such as 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1). Affinity may be measured using the epitope (or a molecule or moiety comprising the epitope) used in the conjugate; alternatively, a similar, non-identical epitope may be used, as long as its affinity may be at least correlated to the affinity of the epitope used in the conjugate, so that a meaningful measurement of affinity may be obtained.

The invention provides methods of treating SLE in an individual, comprising administering to the individual a conjugate comprising (a) a non-immunogenic valency platform molecule and (b) two or more polynucleotides which specifically bind to an antibody from the individual which specifically binds to double stranded DNA, said polynucleotide comprising, consisting essentially of, or consisting of the double stranded sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1), wherein the apparent equilibrium dissociation constant (K_D') for the polynucleotide in the conjugate with respect to the antibody from the individual before or upon initiation of treatment is less than about 1.0 mg IgG per ml, and wherein said K_D' value is used as a basis for selecting the individual to receive the treatment. In other embodiments, the K_D' is less than about any of the following: 0.8; 0.7; 0.6; 0.5; 0.4; 0.3; 0.2; 0.1; 0.09; 0.08; 0.07; 0.06; 0.05;

0.025. These values for K_D' apply to all methods in which K_D' is assessed (including treatment and/or screening), such as those in which treatment based on 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1) is contemplated. In some embodiments, K_D' is less than about 0.8 mg IgG per ml. In some embodiments, K_D' is less than about 0.5 mg IgG per ml. In some embodiments, K_D' is less than about 0.1 mg IgG per ml. Methods of measuring K_D' are described below. Measurement of affinity, either represented by measuring K_D' or by some other method, either before or during treatment is strong, if not conclusive, indication that this parameter was a basis for selecting the individual to receive treatment.

In some embodiments, the invention provides methods of treating SLE in an individual, comprising: (a) assessing before or upon initiation of treatment an apparent equilibrium dissociation constant (K_D') for a dsDNA epitope (including a molecule comprising a dsDNA epitope), preferably a polynucleotide in or of a conjugate with respect to antibodies from the individual which specifically bind to double stranded DNA, said conjugate comprising (a) a non-immunogenic valency platform molecule and (b) two or more DNA epitopes, preferably polynucleotides, which specifically bind to an antibody from the individual which specifically binds to double stranded DNA, said polynucleotide (if that is the dsDNA epitope used) preferably comprising, consisting essentially of or consisting of the (double stranded, or ds) sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1), wherein the individual is selected to receive the treatment if the K_D' is less than about 1.0 mg IgG per ml; and (b) administering to the individual the conjugate, preferably in an amount sufficient to increase the K_D'. In other embodiments, the K_D' is less than about any of the following: 0.8; 0.7; 0.6; 0.5; 0.4; 0.3; 0.2; 0.1; 0.09; 0.08; 0.07; 0.06; 0.05.; 0.025. Methods of measuring K_D' are described below.

In other embodiments, the invention provides methods of treating SLE in an individual, comprising: (a) assessing before or upon initiation of treatment an apparent equilibrium dissociation constant (K_D') for a dsDNA epitope, preferably a polynucleotide in or of a conjugate with respect to antibodies from the individual which specifically bind to double stranded DNA, said conjugate comprising (a) a non-immunogenic valency platform molecule and (b) two or more such epitopes, preferably polynucleotides, which

specifically bind to an antibody from the individual which specifically binds to double stranded DNA, said polynucleotide (if used) comprising, consisting essentially of or consisting of the (ds) sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1); and (b) administering to the individual the conjugate in an amount sufficient to increase the K_D', wherein treatment is continued if K_D' is increased at least about 20% compared to K_D' before or upon initiation of treatment. For these embodiments, a K_D' measured after initiation of treatment (for comparison to K_D' before or upon initiation of treatment) is measured at least about 4 weeks, preferably at least about 6 weeks, more preferably at least about 10 weeks, more preferably at least about 12 weeks, after initiation of treatment. We observed a large range of change in antibody affinity upon treatment over a treatment population (Fig. 5). Accordingly, in other embodiments, treatment is continued if K_D' is increased at least about any of the following (as compared to K_D' before or upon initiation of treatment): 40%, 50%, 75%, 100%, 200%, 500%. Methods of measuring K_D' are described below.

Please substitute the following beginning with paragraph 2 on page 28, line 21 and ending on page 29, line 7.

Accordingly, the invention provides methods of treating lupus nephritis in an individual, comprising administering to the individual a conjugate comprising (a) a non-immunogenic valency platform molecule and (b) two or more polynucleotides which specifically bind to an antibody from the individual which specifically binds to double stranded DNA, said polynucleotide comprising, consisting essentially of, or consisting of the (ds) sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1), wherein the apparent equilibrium dissociation constant (K_D') for the polynucleotide in the conjugate with respect to the antibody from the individual before or upon initiation of treatment is less than about 1.0 mg IgG per ml, and wherein said K_D' value is used as a basis for selecting the individual to receive the treatment. In other embodiments, the K_D' is less than about any of the following: 0.8; 0.7; 0.6; 0.5; 0.4; 0.3; 0.2; 0.1; 0.09; 0.08; 0.07; 0.06 0.05; 0.025. Methods of measuring K_D' are described below. Measurement of affinity, either represented by measuring K_D' or by some other method, either before or

during treatment is strong, if not conclusive, indication that this parameter was a basis for selecting the individual to receive treatment.

Please substitute the following beginning with paragraph 2 on page 30, line 8 and ending on page 31, line 10.

Accordingly, in some embodiments, the invention provides methods of identifying an individual who may be suitable for treatment for SLE, said treatment comprising administration of a conjugate comprising (a) a non-immunogenic valency platform molecule and (b) two or more dsDNA epitopes, preferably polynucleotides which specifically bind to an antibody from the individual which specifically binds to double stranded DNA, said polynucleotide (if a polynucleotide is used) comprising, consisting essentially of or consisting of the (ds) sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1), said method comprising measuring the apparent equilibrium dissociation constant (K_D') for the polynucleotide in (or of) conjugate before or upon initiation of treatment and anti-double stranded DNA antibodies from the individual, wherein an individual is identified by K_D' (or its functional equivalent) of less than about 1.0 mg IgG per ml. In other embodiments, the K_D' is less than about any of the following: 0.8; 0.7; 0.6; 0.5; 0.4; 0.3; 0.2; 0.1; 0.09; 0.08; 0.07; 0.06 0.05; 0.025. The invention thus provides screening based on any of a number of dsDNA epitopes contemplated for use in treatment. Generally, a higher affinity "cut-off" (for example, as indicated by a lower K_D' value) would provide a higher degree of certainty with respect to likely success of treatment.

In other embodiments, the invention provides methods of identifying an individual who may be unsuitable for treatment for SLE, said treatment comprising administration of a conjugate comprising (a) a non-immunogenic valency platform molecule and (b) two or more dsDNA epitopes, preferably polynucleotides which specifically bind to an antibody from the individual which specifically binds to double stranded DNA, said polynucleotide (if used) comprising, consisting essentially of or consisting of the (ds) sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1), said method comprising measuring the apparent equilibrium dissociation constant (K_D')

for the polynucleotide in (or of) conjugate and anti-double stranded DNA antibodies from the individual before or upon initiation of treatment, wherein an individual is identified by K_D' of more than about 1.0 mg IgG per ml. In other embodiments, the individual is identified by a K_D' of more than about 0.8 mg IgG per ml. If expressed as a range, the upper limit may be any number, including, but not limited to, about 2.0, about 3.0, about 5.0, about 10, about 15, about 20.

Please substitute the following beginning with paragraph 4 on page 35, line 23 and ending on page 36, line 2.

For purposes of this invention, the treatment methods used entail a conjugate comprising an non-immunogenic valency platform molecule and at least two (i.e., two or more) dsDNA epitopes, preferably polynucleotides which bind to anti-dsDNA antibody from the individual. Preferably, the polynucleotide is double stranded DNA, preferably the sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1). In some embodiments, the polynucleotide comprises this sequence ($(GT)_{10}$), or consists essentially of this sequence.

Please substitute the following beginning with paragraph 1 on page 49, line 7 and ending on page 49, line 23.

The invention also provides kits for measuring antibody affinities for use in the methods described herein, particularly affinity for an epitope which binds to anti-ds DNA antibodies. Accordingly, the invention includes kits containing (*i.e.*, comprising) one or more dsDNA epitopes, preferably polynucleotides (preferably, double stranded (ds) DNA molecules) comprising an epitope which binds to an anti-ds DNA antibody from an individual (and the epitope-containing polynucleotide binds to an anti-ds DNA antibody from an individual). Accordingly, the kits comprise a molecule or moiety comprising a ds DNA epitope, such as any described herein. In one embodiment, the kit comprises a polynucleotide with (comprising) the sequence (or, alternatively, consisting essentially of or consisting of the sequence) 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1).

Kits comprising a polynucleotide(s) or any other suitable ds DNA epitope may further include instructions for using the polynucleotide to detect affinity of an individual's anti-ds DNA antibody(ies) for the polynucleotide (or ds DNA epitope). In other embodiments, the kits comprise the conjugates described herein, with instructions for using the conjugate to detect affinity of an individual's anti-ds DNA antibodies for the conjugate. Preferably, the conjugate is LJP 394.

Please substitute the following beginning with paragraph 1 on page 50, line 11 and ending on page 51, line 4.

Generally, the dsDNA epitope(s) of the kit, preferably a polynucleotide(s) of the kit (whether in free form or attached to a conjugate or other matrix), contains, or alternatively consists of, the epitope that will be or is used in treatment, or has been demonstrated to have about the same affinity for an individual's anti-ds DNA antibodies as the epitope(s) that will be used in treatment. In other embodiments, the kits comprising a ds DNA epitope whose affinity for anti-dsDNA antibodies mimics or alternatively can be correlated to that of the dsDNA epitope to be used in treatment, such as 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1). These dsDNA epitopes can be used as "proxies" for the ds DNA epitope to be used in treatment, such as LJP 394, in assessing antibody affinity for the methods described herein.

Any appropriate means for detecting binding of the antibodies may be employed (and provided in the kits) such as a labeled anti-human antibody, when the presence of human anti-dsDNA antibodies is tested, wherein the label may be an enzyme, fluorophore, chemiluminescent material radioisotope or coenzyme. Generally, the label used will be an enzyme. Accordingly, in some embodiments, the kit(s) of the invention further comprises a label. In some embodiments, the polynucleotide in the kit(s) is conjugated to biotin. In a preferred embodiment, the dsDNA epitope (such as a polynucleotide, for example, double stranded DNA) is biotinylated. Biotinylation may also be accomplished using commercially available reagents (*i.e.*, Pharmacia; Uppsala, Sweden). In another preferred embodiment, the biotinylated dsDNA epitope comprises,